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Cardiac Involvement in Churg-Strauss Syndrome

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Objective. **Churg-Strauss syndrome (CSS) is a rare form of systemic vasculitis. Previous studies showing cardiac involvement in CSS patients were limited in the number of patients and were often based solely on clinical manifestations. The aim of the present study was to determine in detail the incidence of cardiac involvement in a large population of ambulatory CSS patients.**

Methods. **Thirty-two consecutive patients with CSS in remission (mean ± SD duration of disease between diagnosis and enrollment 6.1 ± 5.8 years, mean ± SD age 61 ± 10 years) who were previously unaware of cardiac involvement were compared with 32 randomly selected age- and sex-matched control subjects, using clinical evaluation, electrocardiography (EKG), echocardiography, and cardiac magnetic resonance imaging (MRI).**

Results. **Detailed cardiac evaluation revealed a 62% prevalence of cardiac involvement in CSS patients compared with 3% in controls ($P < 0.001$), with clinical symptoms in 26% and 3%, respectively ($P = 0.009$), EKG abnormalities in 66% and 3%, respectively ($P < 0.001$), and echocardiographic defects in 50% and 3%, respectively ($P < 0.001$). Cardiac MRI detected cardiac manifestations in 62% of CSS patients. In the presence of cardiac MRI abnormalities, echocardiography could detect cardiac involvement with a sensitivity of 83% and a specificity of 80%. The absence of symptoms or EKG abnormalities did not exclude cardiac involvement, because abnormalities could still be detected in 38% of these patients at the time of echocardiography or cardiac MRI.**

Conclusion. **These results demonstrate a high incidence of cardiac involvement in CSS patients. Systematic cardiac evaluation including detailed imaging is required to properly identify CSS patients with cardiac involvement.**

Churg-Strauss syndrome (CSS) is a rare form of systemic vasculitis that was first described in 1951 (1). Classically, it is characterized by extravascular granulomas and necrotizing vasculitis affecting the small vessels. The major clinical manifestations are asthma, hypereosinophilia, and extrapulmonary manifestations of systemic vasculitis (2). Because of the frequent occurrence of antineutrophil cytoplasmic antibodies (ANCAs) and clinical and histopathologic abnormalities, CSS has been classified along with Wegener's granulomatosis (WG) and microscopic polymyositis as one of the ANCA-associated vasculitides (3). The cardiac manifestations in CSS are highly variable, ranging from (peri)myocarditis, heart failure, myocardial infarction, and pericardial effusion to cardiac tamponade (4–7). When these manifestations are present, they are associated with a worse prognosis (6,8–12).

Considering the potential adverse outcomes associated with cardiac involvement in CSS, early detection is of clinical importance. Unfortunately, due to its often subclinical course as a result of silent infiltration, cardiac pathology might be underdiagnosed by clinicians. Until now, the described incidence of cardiac involvement has largely varied, ranging from 17% when using electrocardiography (EKG) only, to up to 92% in postmortem trials (4–7,13,14). However, these studies

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lack thorough cardiac evaluation, include patients with varying disease activity, and are based mostly on clinical manifestations without detailed cardiac imaging. Two previous studies assessed cardiac involvement using echocardiography in a relatively small number of patients (15,16). In addition, systematic use of cardiac magnetic resonance imaging (MRI) to evaluate cardiac involvement in a population of ambulatory patients with CSS has not previously been done, despite case reports illustrating its possible value for early and accurate detection of myocardial inflammation and fibrosis in CSS patients (17–19).

Thus, the aim of this study was to shed further light on the incidence of cardiac involvement in a population of ambulatory patients with CSS without previous in-depth cardiac screening. Thirty-two CSS patients were compared with randomly selected age- and sex-matched control subjects, using detailed outpatient cardiac evaluation.

PATIENTS AND METHODS

CSS patients. Patients were enrolled at the Maastricht University Hospital from August 2006 to June 2008. Ambulatory patients with previously diagnosed CSS who attended our clinical immunology outpatient department were invited to participate in this study. We included all patients who responded to the invitation and whose disease was in a clinically stable phase. All CSS patients fulfilled the Chapel Hill Consensus Conference criteria for vasculitis (20) and the American College of Rheumatology criteria for CSS (21). Furthermore, by using a recently developed vasculitides algorithm, all patients were classified as having CSS (22). Patients were treated according to a standardized protocol (23). This consisted of prednisolone (1 mg/kg body weight) daily with a maximal oral prednisolone dosage of 60 mg/day. After 4–6 weeks, the daily prednisolone dose was tapered by 10 mg every 2 weeks until the dose reached 30 mg, and thereafter by 5 mg every 2–4 weeks. Cyclophosphamide (2 mg/kg body weight daily) was added in patients with renal involvement, mononeuritis, and/or other severe organ involvement. Once remission was achieved, oral cyclophosphamide was stopped and replaced by azathioprine, or, in case of azathioprine intolerance, by mycophenolate mofetil maintenance therapy. In the year prior to cardiac assessment, 24 of 32 patients (75%) were receiving maintenance corticosteroid therapy, with an average dosage of $<$10 mg/day, and 13 of 32 patients (41%) were receiving maintenance immunosuppressive therapy.

Disease activity was assessed using the Birmingham Vasculitis Activity Score (BVAS) (24), as recommended (25). Disease features were considered only when they were attributable to active vasculitis. All patients were seen by a vasculitis specialist (PvP or JWCT). A detailed clinical history was obtained, and a routine physical examination and standard blood tests were performed. Cardiac assessment included 12-lead EKG, transthoracic echocardiography, and cardiac MRI. Twenty-four hour Holter monitoring, coronary angiography, or endomyocardial biopsies were performed only upon indication, clinical symptoms, and echocardiographic and/or cardiac MRI findings. Cardiac involvement is characterized by conduction disturbances, pericardial effusion, myocarditis, focal myocardial fibrosis and/or edema, wall motion abnormalities, significant valvular regurgitation ($\geq$grade 3), or pulmonary hypertension.

Control subjects. Control subjects matched for age (mean $\pm$ SD age 61 $\pm$ 10 years) and sex (22 men) were randomly selected from a preexisting family-based population from a geographically similar area as part of the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO) (26). The protocol of the FLEMENGHO study was approved by the Ethics Committee of the University of Leuven, Leuven, Belgium. A sample was randomly selected from a population of 480 control subjects and stratified by age and sex. A detailed medical history had been collected previously. Subjects underwent a physical examination, routine blood analyses, 12-lead EKG, and transthoracic echocardiography (27).

Detection and classification of myeloperoxidase (MPO) ANCAs. ANCAs were detected by a combination of indirect immunofluorescence assay and enzyme-linked immunosorbent assay (ELISA) for MPO ANCAs and proteinase 3 ANCAs (28). Results obtained by direct ELISA were confirmed by capture ELISA (28,29).

EKG. A standard resting 12-lead EKG was recorded and analyzed by 1 experienced physician (RMD) who was blinded to patient details. All EKGs were inspected visually to detect technical errors, missing leads, and inadequate quality, and findings were divided into minor and major abnormalities (30). Criteria for minor EKG abnormalities were any of the following: first- and second-degree atrioventricular block, prolonged ventricular repolarization, isolated minor Q and ST-T abnormalities (low-amplitude T waves and abnormally inverted T waves), left ventricular (LV) hypertrophy without ST-T abnormalities, and fascicular blocks. Major EKG abnormalities were defined by the following: high-degree atrioventricular dissociation, left or right bundle-branch block, indeterminate conduction delay, LV hypertrophy with ST-T abnormalities, and presence of arrhythmias (e.g., atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia).

Transthoracic echocardiography. Echocardiographic examinations were performed in standard parasternal, apical, and subxiphoidal views according to the recommendations of the American Society of Echocardiography (31), using a Sonos 5500 from Philips Medical Systems (Best, The Netherlands). The following dimensions were measured: LV end-diastolic diameter (EDD), LV end-systolic diameter, and end-diastolic thickness of the septum and LV posterior wall. LV end-diastolic volume and end-systolic volume (ESV) were obtained from the apical 4- and 2-chamber views by the modified Simpson's method. The LV ejection fraction (LVEF) was calculated in a standard manner and was used to assess global LV systolic function. Right ventricular (RV) size and function were evaluated qualitatively. RV systolic pressure was estimated based on the modified Bernoulli equation and was considered to be equal to the systolic pulmonary artery pressure (sPAP) in the absence of RV outflow obstruction:

Table 1. Baseline characteristics of the CSS patients and control subjects*

	CSS patients (n = 32)	Control subjects (n = 32)	*P*
Age, mean ± SD years	61 ± 10	61 ± 10	NS
Men/women	22/10	22/10	NS
Years since diagnosis of CSS, mean ± SD	6.1 ± 5.8	NA	–
BVAS, mean ± SD, 0–6	0 ± 0	NA	–
Prior medical history			
Hypertension	7 (22)	14 (44)	NS
Dyslipidemia	6 (19)	5 (16)	NS
Diabetes mellitus	4 (13)	0 (0)	0.04
Acute coronary syndrome	1 (3)	0 (0)	NS
Medications at enrollment			
Corticosteroids	24 (75)	NA	–
Immunosuppressive agents	13 (41)	NA	–
Beta blockers	7 (22)	6 (19)	NS
Angiotensin receptor blockers or ACE inhibitors	8 (25)	1 (3)	0.01
Vital signs			
Heart rate, mean ± SD beats per minute	72 ± 8	87 ± 14	<0.001
Systolic blood pressure, mean ± SD mm Hg	128 ± 18	131 ± 15	NS
Diastolic blood pressure, mean ± SD mm Hg	76 ± 10	80 ± 8	NS
Laboratory parameters			
Serum creatinine, mean ± SD mmoles/liter	117 ± 92	87 ± 14	NS
Total eosinophil count × 10^6/liter, mean ± SD	2.4 ± 2.2	2.6 ± 2.1	NS
Leukocyte count × 10^9/liter, mean ± SD	8.6 ± 2.3	5.9 ± 2.2	<0.001
CRP level, mean ± SD mg/dl	4.5 ± 5.0	NA	–
MPO ANCA positive at diagnosis	13 (41)	NA	–

* Except where indicated otherwise, values are the number (%) of patients or controls. CSS = Churg-Strauss syndrome; NS = not significant; NA = not applicable; BVAS = Birmingham Vasculitis Activity Score; ACE = angiotensin-converting enzyme; CRP = C-reactive protein; MPO ANCA = myeloperoxidase antineutrophil cytoplasmic antibody.

sPAP (mm Hg) = RV systolic pressure = trans-tricuspid gradient + right atrial pressure (RAP), where trans-tricuspid gradient is $4v^2$ (v = peak velocity of tricuspid regurgitation in meters/second). RAP was estimated based on the variation in the size of the inferior vena cava with inspiration. Abnormalities were reported as wall motion abnormalities, significant valvular regurgitation (grade ≥3), pericardial effusion, pulmonary hypertension (sPAP >45 mm Hg), endocardial defects, and/or obliterated ventricles.

Cardiac MRI. Patients were examined in a supine position with a 1.5T MR scanner (Gyroscan Intera; Philips Medical Systems) equipped with a cardiac software package and a dedicated phased-array surface coil. After survey scans, EKG-gated cine images were acquired for functional analysis during multiple breath holds using a steady-state free precession sequence in 2-chamber–long axis, 3-chamber–long axis, 4-chamber–long axis, and continuous short axis view covering the entire left ventricle. For the detection of myocardial edema or acute inflammation, multislice short axis images were acquired using a dual-inversion black-blood T2-weighted sequence with fat suppression. A Look-Locker sequence was then applied to determine the inversion time for the subsequent late enhancement scan to optimally "null" LV myocardium. A breath-hold multislice T1-weighted 3-dimensional inversion recovery gradient-echo sequence to evaluate the presence of myocardial fibrosis was used to acquire images in short axis, horizontal long axis, and vertical long axis orientation 10 minutes after intravenous administration of 0.2 mmoles/kg gadopentate dimeglumine with an injection rate of 3 ml/second.

MR images were analyzed with commercially available software (CAAS MRV 3.0; Pie Medical Imaging, Maastricht, The Netherlands, and MASS 6.0; Medis Medical Imaging Systems, Leiden, The Netherlands) by 2 independent readers (one of whom was SS) who were blinded to patient details. Abnormalities were reported as wall motion abnormalities, significant valvular regurgitation (grade ≥3), pericardial effusion, endocardial defects, and/or obliterated ventricles. Images were considered to show pathology if localized intramyocardial increased signal intensity on T2-weighted images (edema) and/or delayed contrast enhancement (focal fibrosis) was present.

Statistical analysis. The prevalence of cardiac involvement was calculated and compared between the groups. Categorical variables were assessed using the chi-square test, and continuous variables were compared using Student's unpaired *t*-test. Correlation calculation was performed using Pearson's correlation coefficient. All values are presented as the mean ± SD. *P* values less than 0.05 were considered significant. Statistical analyses were performed using SPSS version 15.0 software (SPSS, Chicago, IL).

RESULTS

Patient data. Thirty-two consecutive CCS patients (mean ± SD age 61 ± 10 years, 22 men) and 32

Table 2. Clinical findings in CSS patients and control subjects*

	CSS patients (n = 32)	Control subjects (n = 32)	*P*
Cardiac symptoms	8 (26)	1 (3)	0.009
Dyspnea (functional class II–III)	5 (16)	–	–
Chest pain	3 (9)	1 (3)	–
Palpitations	2 (6)	–	–
EKG abnormalities	21 (66)	1 (3)	<0.001
Minor	17 (53)	1 (3)	<0.001
Major	4 (13)	0 (0)	0.04
Echocardiographic findings			
LV ejection fraction, mean ± SD %	54 ± 12	66 ± 6	<0.001
LV end-diastolic diameter, mean ± SD mm	50 ± 7	51 ± 5	NS
LV end-systolic diameter, mean ± SD mm	36 ± 9	31 ± 4	0.01
LV mass, mean ± SD grams	191 ± 51	179 ± 46	NS
Wall motion abnormalities	13 (41)	1 (3)	<0.001
Regional	7 (22)	1 (3)	<0.001
Global	6 (19)	0 (0)	<0.001
Valvular abnormalities	4 (13)	0 (0)	0.04
Mitral regurgitation	2 (6)	0 (0)	NS
Aortic regurgitation	1 (3)	0 (0)	NS
Other	4 (13)	0 (0)	0.04
Pericardial effusion	2 (6)	0 (0)	NS
Pulmonary hypertension	2 (6)	0 (0)	NS
Endocardial defect	1 (3)	0 (0)	NS
Obliterated RV	1 (3)	0 (0)	NS
Combined no. of abnormalities on echocardiography (no. of patients)	16 (50)	1 (3)	<0.001

* Except where indicated otherwise, values are the number (%) of patients or controls. CSS = Churg-Strauss syndrome; EKG = electrocardiographic; LV = left ventricle; NS = not significant; RV = right ventricle.

control subjects (mean ± SD age 61 ± 10 years, 22 men) were enrolled in this study. Baseline patient characteristics are reported in Table 1. CSS patients had been diagnosed as having CSS 6.1 ± 5.8 years prior to enrollment. Thirteen patients (41%) were MPO ANCA positive at diagnosis. In patients, the time since the most recent disease activity varied, but at the time of cardiac assessment all patients were classified as having complete remission of disease with a BVAS score of 0. Laboratory findings at assessment revealed a C-reactive protein (CRP) level of 4.5 ± 5.0 mg/dl, a leukocyte count of 8.6 ± 2.3 × 10^9/liter, and a total eosinophil count of 2.4 ± 2.2 × 10^6/liter, compatible with the fact that all patients had clinical remission of disease at the time of assessment. Most patients (75%) were receiving immunosuppressive drugs (prednisolone with or without azathioprine). Only a small percentage of patients received blood pressure–lowering medication (Table 1). The cardiovascular risk profile of both CSS patients and control subjects is summarized in Table 1.

Cardiac evaluation. In the cohort of ambulatory CSS patients with disease in remission, we found a prevalence of cardiac involvement of 62% compared with 3% ($P < 0.001$) in randomly selected age- and sex-matched control subjects. Cardiac evaluation revealed clinical symptoms in 25% of CSS patients, major EKG abnormalities in 13%, echocardiographic defects in 50%, and cardiac MRI abnormalities in 62% (Tables 1–3).

EKG findings. EKG findings revealed abnormalities in 21 CSS patients (66%) and in 1 control subject (3%) ($P < 0.001$) (Table 2). Minor abnormalities, such as T wave abnormalities and/or pathologic Q waves, were seen in 16 (50%) and 2 (6%), respectively, of the CSS patients, while only 1 control subject (3%) had T wave abnormalities. Major abnormalities in CSS patients included atrial fibrillation in 1 patient (3%) and conduction disturbances (right or left bundle-branch block) in 2 patients (6%). Holter recording, performed in 21 patients, revealed an episode of nonsustained ventricular tachycardia (NSVT) of 6 beats in 1 patient (3%).

Cardiac imaging. Cardiac assessment revealed echocardiographic defects in 50% of CSS patients and cardiac MRI abnormalities in 62%, ranging from wall motion disturbances and focal fibrosis to an obliterated right ventricle (Tables 2 and 3). Echocardiography detected cardiac involvement with a sensitivity of 83% and a specificity of 80% when cardiac MRI abnormalities

Table 3. Cardiac MRI and angiography findings in patients with Churg-Strauss syndrome*

Cardiac MRI (n = 29)	
LV ejection fraction, mean ± SD %	51 ± 16
LV end-diastolic volume, mean ± SD ml	168 ± 58
LV end-systolic volume, mean ± SD ml	91 ± 66
LV mass, mean ± SD grams	178 ± 32
Fibrosis	
Regional	7 (21)
Global	1 (3)
Inflammation	1 (3)
Wall motion abnormalities	
Regional	7 (22)
Global	8 (25)
Valvular abnormalities	
Mitral regurgitation	1 (3)
Aortic regurgitation	1 (3)
Other	
Pericardial effusion	2 (7)
Endocardial defect	1 (3)
Obliterated RV	1 (3)
Combined no. of abnormalities on cardiac MRI (no. of patients)	18 (62)
Angiography (n = 13)	
Normal	8 (62)
Wall irregularities	3 (23)
Significant lesion(s)	2 (15)

* Except where indicated otherwise, values are the number (%) of patients. MRI = magnetic resonance imaging; LV = left ventricular; RV = right ventricle.

were present. Conversely, cardiac involvement determined at cardiac MRI showed a sensitivity of 88% and a specificity of 72% when echocardiographic abnormalities were present. When fibrosis on cardiac MRI was excluded, the sensitivity and specificity of echocardiography compared with cardiac MRI were similar (88% and 81%, respectively). Fibrosis on MRI was found only in patients who had other cardiac abnormalities both at echocardiography and cardiac MRI. Significant correlations were found when comparing cardiac MRI with cardiac ultrasound for LVEF ($R = 0.86$, $P < 0.001$), LVESV ($R = 0.86$, $P < 0.001$), LVEDV ($R = 0.87$, $P < 0.001$), and LV mass ($R = 0.66$, $P < 0.001$).

Coronary angiography and histology. A coronary angiogram was obtained in 13 patients with chest pain, dyspnea, and cardiac abnormalities, revealing no stenosis in 8 of the 13 patients (62%). Three patients (23%) had wall irregularities, and 2 patients (15%) showed a lesion (>70% stenosis) in the left anterior descending coronary artery (Table 3). Nine patients underwent endomyocardial biopsies. Five patients had an increase in lymphocyte infiltration (>14 CD45+ T lymphocytes/mm^2) in their biopsy specimens, with associated active lymphocytic myocarditis in 1 patient and eosinophilic infiltrate in another. None of the biopsy specimens showed histologic signs of active vasculitis. In the patient with the episode of NSVT, histologic analysis also showed increased lymphocytic infiltrate.

There was no relationship between the duration of CSS, prior corticosteroid or immunosuppressive therapy, and cardiac manifestations. Seventy-four percent of ANCA-negative patients showed cardiac involvement, and wall motion disturbances were the most frequent finding in up to 64% of the patients. In contrast, cardiac abnormalities could be detected in only 23% of ANCA-positive patients ($P = 0.01$).

Defects were seen at echocardiography or cardiac MRI in 88% of patients who had clinical symptoms and in all patients when major EKG abnormalities were present. In the patients with clinical symptoms, the finding of dyspnea could be clarified by reduced LV function in 2 patients and significant valvular disease in the other 3 patients. Two patients reported palpitations, which were accompanied by atrial fibrillation and coronary artery disease in both. Chest pains reported by 3 patients were associated with coronary artery disease in 2 patients, while 1 of the patients did not have any cardiac abnormalities clarifying the symptoms. In the absence of symptoms and with a normal EKG, cardiac involvement could still be detected at echocardiography or cardiac MRI in 38% of the patients.

There was a significantly greater prevalence of diabetes mellitus (DM) in the CSS patients than in the control subjects. When we excluded these DM patients from the analyses, the results remained similar, revealing abnormal clinical symptoms in 25% of CSS patients compared with 3% of control subjects ($P = 0.01$), major EKG abnormalities in 11% of CSS patients compared with 0% of control subjects ($P = 0.06$), echocardiographic defects in 54% of CSS patients compared with 3% of control subjects ($P < 0.001$), and cardiac MRI abnormalities in 69% of CSS patients.

DISCUSSION

The present study assessed cardiac involvement in a cohort of 32 patients with clinically remissive CSS, using a combination of clinical evaluation, EKG, echocardiography, and cardiac MRI. Our findings reveal a 62% prevalence of cardiac abnormalities in CSS patients compared with 3% in age- and sex-matched control subjects. The high prevalence of cardiac defects was not caused by concomitant cardiac diseases such as coronary artery disease and/or hypertension, since the prevalence of these diseases in our CSS patients was relatively low and comparable with that in the control group (Table 1).

After exclusion of DM from the analysis, the differences in cardiac abnormalities remained similar, suggesting that DM was not a concomitant factor.

CSS is a disease characterized by asthma, hypereosinophilia, and vasculitis. The disease can typically be divided into 3 distinct phases (32). The initial phase of the disease starts with asthma, allergic rhinitis, and nasal polyposis, the second is marked by a period of peripheral and tissue eosinophilia associated with pulmonary infiltrates, and the third is characterized by systemic vasculitis. Involvement of the heart has been described in the third phase as vasculitic lesions in myocardium and the coronary vessels, causing (peri)myocarditis, heart failure, cardiac tamponade, myocardial infarction, or pericardial effusion (4–7). Myocardial damage is caused by vasculitis leading to coronaritis and coronary occlusion, by the release of toxic mediators by activated eosinophils causing direct myocardial damage (33), or by replacement of the myocardium with granulomas and scar tissue (14,34). Pulmonary hypertension secondary to concomitant pulmonary involvement may also induce RV dysfunction (35,36).

In general, the prognosis of CSS is good, with an overall 10-year survival rate of 81–92% (7,11). Cardiac involvement, however, is one of the most important predictors of an adverse outcome, since up to 50% of CSS-related mortality is caused by cardiac involvement (6,11). Of the patients with myocardial involvement, 39% died during the acute phase of their disease (11). Optimal therapy is therefore important, since Cohen et al (37) reported that long-term treatment with adjunctive immunosuppressive agents in patients with a poor prognosis, including cardiac involvement, improved event- and disease-free survival rates. In addition, several studies showed resolution of myocardial manifestations after steroid and/or immunosuppressive therapy (38–40). Thus, early diagnosis of cardiac involvement and subsequent adjunctive therapy may prevent progression of cardiac disease.

Previous reports indicated that ANCA positivity at the time of diagnosis was more often associated with renal involvement, peripheral neuropathy, and biopsy-proven vasculitis, whereas ANCA negativity was associated with heart disease and fever (10,41). Cardiac involvement in our group was seen in 23% of the ANCA-positive patients and in 74% of the ANCA-negative patients. These results are concordant with those of the French Vasculitis Study Group, which found an ANCA-negative status in 62% of CSS patients, with cardiac manifestations in 49% of those patients (41).

Development of accelerated atherosclerosis and resultant ischemic heart disease is an important cause of morbidity and mortality in different systemic autoimmune diseases, including rheumatoid arthritis (RA), systemic sclerosis, systemic vasculitis, systemic lupus erythematosus (SLE), and primary antiphospholipid syndrome (36,42,43). Systemic inflammation and immunologic abnormalities result in accelerated atherosclerosis independent of classic risk factors (44–46). In addition, glucocorticoid therapy causes cardiac dysfunction due to accelerated atherosclerosis and ischemic heart disease but may also increase the incidence of DM and hypertension.

In the present study, blood pressure did not differ significantly between the CSS patients and the control subjects, and the increased incidence of DM in the CSS patients did not solely explain increased cardiac involvement. Atherosclerosis related to cardiac involvement was present in 15% of the CSS patients as detected by coronary angiogram, concordant with cardiovascular involvement in other autoimmune diseases (36,42). Direct cardiac inflammation independent of atherosclerosis is an important cause of disease-associated cardiac injury and dysfunction in different systemic diseases. In our population, we found LV dysfunction in 34% of the CSS patients compared with other systemic diseases such as RA (5%), WG (15%), and SLE (27%) (47–49). Therefore, we conclude that cardiac disease is seen in systemic autoimmune diseases and particularly in CSS. Immunosuppressive therapy, including glucocorticoid treatment, will possibly help to prevent these harmful episodes.

Our results underscore a high incidence of cardiac manifestations in CSS patients during remission of their disease. The clinical history, EKG, echocardiography, and cardiac MRI were the most marked components of the outpatient evaluation for the diagnosis of cardiac involvement. In the absence of symptoms and major EKG abnormalities, cardiac involvement could still be detected in nearly 40% of the patients, indicating that the absence of symptoms or the presence of a normal EKG does not exclude cardiac involvement. We therefore recommend that the evaluation for cardiac involvement in patients with CSS should include not only detailed history of cardiac symptoms and EKG, but also imaging with echocardiography or cardiac MRI. Since CSS with cardiac involvement has been associated with a worse prognosis (6,8–12), early diagnosis is advocated, since appropriate therapy may prevent progression of cardiac disease (37–40).

The present study is cross-sectional, and a longitudinal study would have given additional information

on symptoms present at the time of presentation or during followup. Despite this limitation, this study reveals that systematic cardiac evaluation with detailed imaging in CSS patients is required to properly identify cardiac involvement. In the setting of a multidisciplinary approach to CSS, including evaluation by a cardiologist, our findings reveal a high incidence of cardiac abnormalities in CSS patients who previously were unaware of the presence of such abnormalities.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Heymans had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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